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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/547,532

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Yasushi Shintani

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EXAMINER

MACFARLANE, STACEY NEE

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/547,532	Applicant(s) SHINTANI ET AL.	
	Examiner STACEY MACFARLANE	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12 and 24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/17/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 14, 2009 has been entered.

Response to Amendment

2. Claims 12 and 24 have been amended as requested in the amendment filed on October 14, 2009, entered by way of RCE. Following the amendments, claims 12 and 24 are pending and will be examined in the instant office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 12 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising contacting a cell expressing SEQ ID NO: 8 with SEQ ID NO: 2 in the presence/absence of a test compound and assessing a decrease of about 20% or more in signal transduction or assessing a

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decrease of about 20% or more in binding between SEQ ID NO: 2 and SEQ ID NO: 8, does not reasonably provide enablement for the identification of any specific substance that would be reasonably expected to have brain/nerve cell protective activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

6. In Remarks filed October 14, 2009, Applicant traverses the rejection on the grounds that the specification provides a single example of a substance identified by the method, which has neuroprotective action (Remarks, page 5, first paragraph citing Example 2). Additionally, Applicant argues that any further "screening" required is routine within the art (paragraph bridging pages 5-6). While this has been considered in full it is not persuasive to overcome the rejection for the following reasons.

7. It should be noted that in method claims the preamble of the claim is given weight, thus the instant method is directed to identifying substances with brain/nerve cell protective action. The method steps of the claims, however, do not require the specific use of neuronal cells. Additionally, there is no active step whereby the

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neuroprotective action of the substance identified is confirmed. In order to establish that the method of the claims is enabled, there must be a nexus between what is measured and neuroprotection, however, no such nexus is provided in the disclosure. What is disclosed about the claimed method is narrow. Working Example 2 demonstrates that in vivo intraventricular administration of an MIP-3-alpha-neutralizing antibody decreases infarct volume in a rat model of cerebral ischemia. Examples 3 and 5 provide only a hypothesis that a decrease in MIP-3-alpha or CCR6 expression/activity may be neuroprotective, by demonstrating that MIP-3-alpha and/or CCR6 expression is induced upon ischemic attack and is suppressed by hypothermic treatment, which is well-recognized in the art to be neuroprotective. However, the mere suppression of expression is not a show of causation. Thus, these examples do not establish a clear nexus between the specific method of the claims, comprising detecting decreased signal transduction/binding, and a neuroprotective effect. Thus, one of ordinary skill in the art would rely upon what was known at the time of filing between decreases in signal transduction/binding between MIP 3-alpha and its receptor and neuroprotective effects.

8. The following prior art teaches a method that is identical to the method steps of the invention (see art rejection below; Sullivan et al., Journal of Leukocyte Biology, 66: 674-682, October 1999). Specifically, Sullivan et al. identify pertussis toxin (PTX), the MEK1 and MEK2 inhibitor, PD98059 and LY294002, a PI3 Kinase inhibitor all decrease MIP-3-alpha-induced cell migration, mobilization of calcium stores, and phosphorylation of MAPK. Thus, according to the method of the instant claims, PTX, PD98059 and

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LY294002 would each be identified as a substance that exhibits brain/nerve cell protective action. Yet, there is nothing of record to suggest that PTX, PD98059 and/or LY294002 are neuroprotective. On the contrary, the following art teaches LY294002 as specifically inducing neuronal apoptosis (Habas et al., Journal of Neurochemistry, 96:335-348, 2005). Thus, much unpredictability remains within the art and there is no nexus between decreases in MIP 3-alpha signal transduction/binding and brain/nerve cell protective effects. Absent guidance within the instant disclosure that overcomes the unpredictability within the art, one of ordinary skill would have to make a substantial inventive contribution in order to practice the method commensurate in scope with the claims.

9. The standard of an enabling disclosure is not the ability to make and test if the invention works but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

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10. The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. Therefore, Claims 12 and 24 are rejected under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirement.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 12 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Sullivan et al., Journal of Leukocyte Biology, 66: 674-682, October 1999.

13. Claim 12 is drawn to a method for screening neuroprotective substances comprising measuring and comparing "signal transduction activity" in a cell in the presences or absence of a test compound, wherein the cell expresses SEQ ID NO: 8 (a.k.a. CC chemokine receptor 6 or CCR6) and is contacted by SEQ ID NO: 2 (a.k.a. CCL20 or MIP-3-alpha), and wherein a test compound that decreases "signal transduction activity" by about 20% or more is identified as a candidate compound that exhibits neuroprotective action. Claim 24 is drawn to a method for screening neuroprotective substances comprising measuring and comparing "binding activity" between SEQ ID NO: 2 (a.k.a. CCL20 or MIP 3-alpha) and SEQ ID NO: 8 (a.k.a. CC chemokine receptor 6 or CCR6) in the presence/absence of a test compound, wherein a

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test compound that decreases binding by about 20% or more is a neuroprotective compound. It should be noted that CCR6 receptor demonstrate specificity for binding CCL20 (See attached MeSH datasheet). Regarding "signal transduction activity" the specification states (page 13):

"A measurement of signal transduction activity is conducted according to a method known per se. For example, a stimulatory activity on CCR6-expressing cells (for example, activity to promote or suppress an increase in intracellular cAMP concentration, liberation of intracellular Ca^{2+} , production of inositol phosphate, changes of cell membrane potential, phosphorylation or dephosphorylation of intracellular protein, activation of c-fos, reduction of pH and the like, mediated by CCR6) is measured by a known method."

The Sullivan et al. prior art teach methods comprising contacting cells that natively express CCR6 (Figure 4) with MIP-3-alpha in the presence/absence of test compounds that are inhibitors of intracellular signal transduction pathways, such as pertussis toxin (PTX), PD98059 and LY294002. Specifically, Sullivan et al. teach that PTX, PD98059 and LY294002 inhibit MIP-3-alpha-induced signal transduction activity as assessed by cell migration assay (Figure 1). Additionally, Sullivan et al. demonstrate that MIP-3-alpha-induced intracellular calcium mobilization is completely inhibited by PTX (Figure 2B). Thus, the method of Sullivan et al. explicitly teaches a screening method for substances that have brain/nerve cell protection action and identifies PTX as a substance that specifically decreases signal transduction activity, as defined in the specification as a suppression of "liberation of intracellular Ca^{2+} ", in cells expressing SEQ ID NO: 8 in the presence of SEQ ID NO: 2, and wherein the decrease is specifically "about 20% or more". Additionally, Sullivan et al. demonstrate that the compounds PTX, PD98059 and LY294002 decrease MIP-3-alpha-induced

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phosphorylation of MAPK (Figure 3C), thus, teaching screening of neuroprotective test compounds by identifying those that decrease “signal transduction activity” as defined in the specification as encompassing phosphorylation of an intracellular protein.

Furthermore, Sullivan et al. demonstrate that eotaxin and MCP-4 compete with MIP-3-alpha for binding to CCR6 receptors (Figure 5). Thus, the method of the instant claims fails to distinguish over that disclosed in the Sullivan et al. prior art.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-R 5:45 to 3:30, TELEWORK-Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/
Primary Examiner, Art Unit 1647

Stacey MacFarlane
Examiner
Art Unit 1649